Efficacy and Safety of Aspirin Plus Intermittent Pneumatic Compression Device vs. Low Molecular Weight Heparin as Thromboprophylaxis after Total Hip Arthroplasty: A Prospective Randomized Control Trial

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ABSTRACT

INTRODUCTION: Total hip arthroplasty has notable risk of morbidity and mortality from venous thromboembolic events. The purpose of this study was to find out the incidences of deep vein thrombosis and pulmonary embolism in patients undergoing total hip joint arthroplasty and compare effectiveness and safety of thromboprophylaxis with aspirin plus intermittent pneumatic compression device with that of low molecular weight heparin.

METHODS: Patients who had total hip arthroplasty (unilateral/bilateral) were randomized to receive prophylaxis with aspirin plus intermittent pneumatic compression device or low molecular weight heparin. Routine screening for deep vein thrombosis with color Doppler was performed.

RESULTS: 180 patients (224) joints) were randomized into 2 groups. The rates of deep venous thrombosis were 2.22% in the aspirin plus compression group compared to 0% in the low molecular weight heparin group. The rates of pulmonary embolism were 1.11% in the Aspirin plus compression group and 0% in the heparin group, and there were no fatal pulmonary emboli. Within the six weeks and three months follow-up, no thromboembolic events occurred. The rate of major bleeding events was 1.11% in the aspirin and compression group and 10% in the low-molecular-weight heparin group.

CONCLUSIONS: An inexpensive multimodal protocol, consisting of aspirin, exercises, and the use of intermittent compression devices, was associated with low thromboembolic complications.

KEYWORDS: Aspirin, Deep vein thrombosis, Low molecular weight heparin, Pulmonary embolism, Total hip arthroplasty

LEVEL OF EVIDENCE: Level I

INTRODUCTION

Total hip arthroplasty (THA) is one of the most successful procedures in modern orthopedics that relieves pain, improves function, and enhances the quality of patients' lives. However, this procedure is associated with complications of venous thromboembolic events.[1,2] The reported incidence of distal vein thrombosis after THA without prophylaxis is 40%–70%, proximal DVT is 10%–20%, clinical DVT is 1%–3%, non-fatal symptomatic pulmonary thromboembolism is 1%–2%, and fatal pulmonary thromboembolism 0.1%–1% respectively.[3,4] Johnson et al. in a series of 7959 total hip replacements performed between 1962 and 1973 reported that the overall prevalence of pulmonary embolism was 7.89 percent and that of fatal pulmonary embolism was 1.04 percent.[5]

Similarly, in 1974, Coventry et al. reported an overall prevalence of pulmonary embolism of 2.2 percent in a series of 2012 consecutive total hip replacements. In a subset of 62 patients who had received no prophylactic anticoagulation, the prevalence of fatal pulmonary embolism was 3.4 percent.[6]

Dorr et al. retrospectively reviewed the records on 1179 consecutive total joint arthroplasties in 970 patients who had undergone primary and revision total hip and total knee replacement.[7] 856 patients (1046 operations) were considered to be low risk and were managed with aspirin, dipyridamole, or clopidogrel bisulfate as well as intermittent pneumatic calf compression devices. 144 pts (133 operations) were considered to be high risk and managed with low molecular-weight heparin or warfarin and intermittent calf compression. No fatal pulmonary embolus was detected. 3 nonfatal pulmonary emboli (prevalence, 0.3 percent) were detected in association with the 1046 procedures in the low risk group, and none were detected in association with the 133 operations in the high-risk group ($p = 0.767$). Symptomatic deep venous thrombosis was detected in 4(0.38 percent) of the 1046 operations in the low-risk group and 1 (0.75%) of the 133 operations in the high-risk group ($p = 0.93$).

Chemical prophylactic agents such as aspirin, warfarin, heparin, and pentasaccharides, as well as physical modalities such as compression stockings and lower extremity pumps are used to minimize the risk of VTE.[8]

The widespread belief that the rate of fatal pulmonary embolism after total hip replacement arthroplasty is more than 1% is based on the findings of a few studies conducted mainly in the 1960s and 1970s.[9,10] During the last decade, the incidence of fatal PE has decreased substantially to a rate of 0% to 0.2%.[9,10] This reduction is the result of advancements in anesthesia and surgical technique, our better understanding of the pathogenesis of thromboembolic disease during and after surgery, use of pneumatic compression devices, better pain management, and early mobilization. This incidence appears to be consistent no matter which prophylactic agents are used.[10]

Among Asians, particularly Indian population, it has been said anecdotally that there is a considerably lower prevalence of deep vein thrombosis.[11,12]

MATERIALS AND METHODS

180 patients (224 joints) were enrolled after informed and written consent and prospectively followed and studied from May 2010 to May 2012 in the department of Orthopedics, All India Institute of Medical Sciences. Prior approval for the study was obtained from the Institutional Ethics Committee.

All the patients who were scheduled for unilateral or bilateral total hip arthroplasty were included in the study. Exclusion criteria included patients with coagulation or bleeding disorders, hypersensitivity to aspirin or low molecular weight heparin, Heparin induced thrombocytopenia, history of thromboembolic disease/ chronic venous insufficiency, ocular or neurosurgical procedure during last 3 months, active peptic ulcer disease, severe renal insufficiency, systolic hypertension >200 mm Hg, pulmonary tuberculosis, a solid malignancy tumor, active Liver disease, and peripheral vascular disease.

All the eligible patients were randomized either to receive enoxaparin 40mg once a day s/c 12 hours after surgery after removal of epidural catheter (if present) till patient was mobilized (approximately 4th postoperative day) or aspirin 325 mg twice a day for 6 weeks along with intermittent pneumatic compression device applied within 2 hours of surgery till patient was mobilized (approximately 4th postoperative day).

Patients in both groups were closely monitored throughout their hospitalization for any potential

bleeding complications and for clinical signs and symptoms of deep venous thrombosis or pulmonary embolus. After four to seven days (earlier if clinically indicated), all patients underwent bilateral lower-extremity duplex ultrasonography to screen for deep venous thrombosis. A cardiologist evaluated any clinical symptoms suspicious of pulmonary embolism and a battery of tests including electrocardiogram, chest x-ray, arterial blood gas analysis, and Pulmonary CT angiography were run. Experienced radiologist of Department of Radio-diagnosis performed color Doppler screenings. Both cardiologists and radiologists were blinded with respect to the nature of DVT prophylaxis received by the patients.

A patient who had distal vein thrombosis on Color Doppler was evaluated daily for symptoms/signs of propagation and PE. Repeat Doppler was done after 4 days and before hospital discharge. A patient with proximal vein thrombosis was treated with Enoxaparin 1mg/kg twice daily (at least for 5 days and discontinued when INR >2 on 2 consecutive measurements at least 24 hrs apart) along with Warfarin 5 mg for period of 3 months. Serial Doppler studies were done to document the resolution of thrombus. If thrombus was found to be propagating or unresolved, CT pulmonary angiography was done.

All patients with a negative scan were followed clinically, for a mean (and standard deviation) of 10 ± 2 weeks, for signs or symptoms of deep venous thrombi, pulmonary emboli, or re-hospitalization because of a complication related to the method of prophylaxis, a bleeding complication, or a wound problem. Repeat Color Doppler of B/L lower extremity was done at 6 ±1 weeks follow up (earlier if clinically indicated). The duration of follow-up was limited to a period of three months.

The primary determinant of efficacy of thromboprophylaxis was the incidence of DVT as determined by Color Doppler study of the bilateral lower extremity and clinical evidence. Clinical evidence included reported DVT /PE as an adverse event or the occurrence of symptoms and signs of thromboembolic disease and associated therapy. Color Doppler diagnosed DVT was the primary end point for determination of efficacy of study.

The primary determinants of safety were the incidences of major and minor hemorrhagic episodes. A major hemorrhagic episode was defined as overt hemorrhage associated with anemia that required prolonged hospitalization, anemia with hypotension that required intervention to prevent impairment, bleeding that required any intervention such as surgery or hematoma aspiration to prevent permanent impairment or damage, bleeding that endangered critical organs (intracerebral, intraocular, intraspinal, pericardial, or retroperitoneal), hematoma that required prolonged hospitalization, hematoma that led to joint infection requiring debridement, death or a life-threatening clinical event, postoperative transfusion of more than two units of packed red blood cells, decrease of 20 g/l or more in hemoglobin that is directly attributable to the overt hemorrhagic episode.

Minor bleeding was any bleeding that was not major bleeding (e.g., increased wound drainage reported by the surgeon or a drop in the hemoglobin level not requiring transfusion or prolonged hospitalization). The bleeding index (defined as the number of units of whole blood or packed red blood cells transfused plus the difference between the first hemoglobin value after surgery and the value prior to discharge), a decrease in the hemoglobin level of ≥20 g/l, and the number of units of blood transfused were reported.

STATISTICAL ANALYSIS

The Fisher exact test was used for the sample-size calculation with an estimated effect size of 4%. Demographics were compared to ensure that the randomization process had resulted in similar patient characteristics between

groups. Chi-square tests were used to assess group differences in categorical variables, and independent t tests were used to compare continuous variables.

The Fisher exact test was used to compare the primary variable of safety, the frequency of major bleeding events, between the groups. Other bleeding data were compared between the groups as well. Categorical variables (the proportion of patients with a drop in the hemoglobin level of ≥20 g/L and the proportion of those who had a bleeding index of ≥2) were examined with use of the chi-square test. Continuous variables (the mean number of units of blood transfused and the mean bleeding index) were analyzed with use of independent tests or the Mann-Whitney U test when appropriate. The secondary variable of efficacy and the frequency of venous thromboembolic events were compared between groups by using a chi-square test. All tests were two-tailed, and the alpha level was set at 0.05.

RESULTS

Of 180 patients enrolled from May 2010 to May 2012, 90 patients were enrolled in the low-molecular-weight heparin group (Group A) and 90 were in aspirin + intermittent pneumatic compression group (Group B). Not a single attrition was reported at the follow-up period of 3 months. Demographics were similar clinically in the two groups. [Table 1]

9 patients (10%) in group A and 1 (1.11%) in Group B had major bleeding events and this difference was statistically significant (p=0.019). [Table 2]

47 patients (52.22%) in group A and 17 (18.89%) in Group B had episodes of minor bleeding events, which was statistically significant (p=0.001). Though there were considerable differences between rates of major bleeding events, except for hematoma requiring prolonged hospitalization and PRBC units transfused, no finding was statistically significant. [Table 3]

Table 1: Demographics features of cases enrolled in the study.

	Group A (N=90)	Group B (N=90)	Range	P value
Male sex	51	48		
Female sex	39	42		
Mean age (yr)	49.08	48.26	19-85	0.340
Weight (kg)	65.39	63.83	45-110	0.063
Diagnosis of inflammatory arthritis (%)	20	26.67		0.400
Unilateral joint (%)	61.20	59.63		0.403
Bilateral joint (%)	37.93	40.37		0.606
Regional anesthesia	83	81		0.637
General anesthesia	7	9		0.637
Mean duration of surgery (min)	95.28	94.76	45-190	0.400
Mean intraoperative blood loss (ml)	351	358.33	150-700	0.653

Table 2: Major bleeding events in the two groups

	Group A (LMWH)	Group B (Aspirin + IPC)	P value
No. of patients with PRBC transfusion ≥2 units	29 (32.22%)	15 (16.67%)	0.033
No. of patients with mean Hb change ≥ 20 g/l	9 (10%)	4 (4.44%)	0.256
Hematoma requiring prolonged hospitalization	9 (10%)	1 (1.11%)	0.019
Hematoma requiring debridement	4 (4.44%)	0	0.122
Anemia with hypotension	3 (3.33%)	1 (1.11%)	0.622
Intracranial bleeding	0	0	
Epidural hematoma	0	0	
Retroperitoneal bleeding	0	0	
Gastrointestinal bleeding	0	0	
Urinary bleeding	0	0	
Myocardial Infarction	1	0	1
Heparin induced Thrombocytopenia	0	0	

Table 3: Minor bleeding events in the two groups

	Group A	Group B	P value
Bruises	47 (52.22%)	17 (18.89%)	0.001
Prolonged discharge	27 (30%)	7 (7.78%)	0.001
Cellulitis	16 (17.78%)	5 (5.56%)	0.0013

A total of 2 (1.11%) deep vein thrombi were detected by bilateral color Doppler study. Both the patients had popliteal vein thrombi, both were enrolled in Group B (2.22%). No patient enrolled in Group A had ultrasonography detected deep vein thrombosis (p=0.498). Both were treated with warfarin 5mg and enoxaparin 1mg/kg twice daily, dosage titrated to achieve target INR 2. Both the patients had serial color Doppler done every 4 days, twice during their hospital discharge and were followed every 2 weeks. There was no propagation of thrombi and popliteal thrombi dissolved after 1 month in both the patients. No patients of either group had ultrasonography detected DVT after 6 week and 3 month follow-up.

One (0.56%) patient had sudden onset dyspnea, tachypnea, tachycardia, and Pulmonary CT angiography proven pulmonary embolism (PE). The patient was enrolled in Group B. The patient was started on warfarin 5mg (eventually for period of 3 month) and enoxaparin 1mg/kg twice daily for period of 10 days. There was no

mortality from pulmonary embolism. Repeat color Doppler studies after 2 week, 6 week, and 3 month was normal.

DISCUSSION

In our prospective study involving 180 patients (224 joints) undergoing THA, we found the incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) in to be very low. Two (1.11%) patients out of 180 patients had popliteal vein thrombosis, one (0.55%) patient developed symptomatic pulmonary embolism, and none had fatal thromboembolic event. Both the patients with DVT and one patient with symptomatic PE were enrolled in Group B. No patient enrolled in Group A had any thromboembolic events. These results correspond favorably to those reported by Indian studies in literature.[11,12]

We powered the study for an evaluation of safety instead of an assessment of efficacy for two reasons. First, practicing orthopedic surgeons are deeply concerned about bleeding issues associated with any of the utilized prophylactic drugs. This is demonstrated in the recent American Academy of Orthopaedic Surgeons guidelines for prophylaxis against symptomatic pulmonary embolism following total hip arthroplasty.[13] Second, clinically relevant thromboembolic events are so rare that statistically significant changes would be difficult to demonstrate. To show significance ($p<0.05$ at power 80%) in reducing the prevalence of PE 1% to 0.5%, would require more than 10,000 patients.[10] So, the performance of a prospective, Single center trial to assess pulmonary embolism-related death would require > 50,000 patients, making it a practical impossibility.[10]

The 1.11 percent prevalence of symptomatic, nonfatal pulmonary embolism compares favorably with the rates of 0.7 percent for patients managed with low-molecular- weight heparin (in a meta-analysis of 2065 patients in twenty studies) and 2.7 percent for those managed with warfarin (in meta-analysis of 864 patients in ten studies). [14]

Literatures comparing LMWH and compression device plus aspirin are very rare.[15,16,17,18] Our findings with regard to venous thromboembolic events support those in a previously reported study comparing a compression device plus aspirin with low-molecular-weight heparin.[15] In that study, Clifford et all [15]found of major bleeding events was 0% in the compression group and 6% in the low-molecular-weight heparin group. The rates of distal and proximal deep venous thrombosis were 3% and 2%, respectively, in the compression group compared with 3% and 1% in the heparin group. The rates of pulmonary embolism were 1% in the compression group and 1% in the heparin group, and there were no fatal pulmonary emboli.

In our study, the risks of major bleeding events (1.11%) and minor bleedings events (18.89%) with the use aspirin plus intermittent pneumatic compression devices were substantially lower than 10 percent risk of major bleeding events and 52.22 percent risk of minor bleeding events with LMWH use in our study and those reported in literature.[19,20]

Our study was limited because the number of patients was not adequate to delineate the difference in efficacy between the two methods of prophylaxis.

CONCLUSIONS

The incidence of thromboembolic events in Asian patients undergoing hip arthroplasty is substantially lower than their western

counterparts.[11,12] Also, significant is the fact that the global threat of thromboembolic events after total joint arthroplasty has been substantially reduced during the past decade.[9,10] The risk of deep vein thrombosis (DVT) in our study is 1.11%, that of symptomatic pulmonary embolism (PE) 0.56%, and 0% for fatal thromboembolic events. The worldwide risk of fatal pulmonary embolism is 0.1%. This reduction in risk is due to confluence of changes in our medical practices including early mobilization, more efficient and less traumatic surgical procedures, better pain management, and use of regional anesthesia.[9,10]

Our data suggest that an inexpensive multimodal protocol, consisting of aspirin, exercises, and the use of intermittent compression devices, was associated with few thromboembolic complications.

Our study does not allow us to state that the administration of aspirin and compression device was totally responsible for the low rate of thromboembolic complications. It is likely that the use of regional anesthesia, less traumatic surgery (meticulous dissection, highly experienced surgeon, and less operative time) , and an intensive postoperative program of physical exercises were also important contributors to its low incidence.

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